



Antimigraine Agents, Other Therapeutic Class Review (TCR)

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MANAGEMENTSM

FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
erenumab-aooe (Aimovig™) ¹	Amgen	Preventive treatment of migraine in adults
fremanezumab-vfrm (Ajovy®) ²	Teva	Preventive treatment of migraine in adults
galcanezumab-gnlm (Emgality®) ³	Eli Lilly	Preventive treatment of migraine in adults

OVERVIEW

Headache is one of the most common complaints by patients when presenting to a physician. Migraine accounts for 10% to 20% of all headaches in adults and affects over 39 million men, women, and children in the United States (US).^{4,5} It is estimated that 18% of women, 6% of men, and 10% of children experience migraine.^{6,7} Migraine is the 12th leading cause of years lived with disability among females of all ages.⁸ The American Migraine Study 2 found that migraine causes decreased productivity and absenteeism from work for many patients, which creates a large economic impact for the US.⁹ Approximately 85% of patients with migraine headaches suffer less than 3 to 4 attacks per month.¹⁰ The median frequency of migraine attacks among migraine sufferers is 1.5 per month.¹¹

Migraine is a complex neurological condition that can involve debilitating headache and sensory changes.¹² During a migraine attack neurologic changes occur in the cortex, brainstem, hypothalamus, thalamus, as well as, peripheral and central portions of the trigeminovascular system. Migraine attacks are usually episodic, occurring < 15 days per month, but some migraine sufferers experience chronic daily headaches ≥ 15 days per month, often with migrainous features. Key features for the diagnosis of migraine headache includes an episodic headache lasting 4 to 72 hours with at least 2 of the following symptoms: unilateral pain, throbbing, aggravated by routine physical activity, pain of moderate to severe intensity.¹³ During the migraine at least 1 of the following are present: nausea and/or vomiting, or photophobia and/or phonophobia.

Non-opioid analgesia with a nonsteroidal anti-inflammatory drugs (NSAIDs), or combinations such as aspirin or acetaminophen plus caffeine, are recommended as first-line therapy for patients with mild to moderate migraine pain.¹⁴ Due to well-established efficacy, the triptans have become the drugs of choice for treating migraine attacks. Response rate to triptans is about 60%. Studies suggest that 38% to 50% of migraineurs are candidates for preventive therapy.¹⁵ Indications for preventive therapy include ≥ 4 migraine attacks per month or ≥ 8 migraine days per month; acute medication overuse; and debilitating migraine.^{16,17} The 2012 (reaffirmed in 2015) practice guidelines by the American Academy of Neurology (AAN) and the American Headache Society (AHS) advise that antiepileptic drugs (divalproex sodium, sodium valproate, topiramate) and beta-blockers (metoprolol, propranolol, timolol) are established as effective in migraine prevention (Level A).¹⁸ Frovatriptan is established for short-term menstrually associated migraine (MAM) prevention (Level A). Naratriptan, zolmitriptan (both for short-term MAM), antidepressants (amitriptyline, venlafaxine), and beta-blockers (atenolol, nadolol) are probably effective in migraine prevention (Level B); however, no triptan is approved for the prevention of migraines. While there is a wide variety of agents to consider for episodic migraine prevention, side effects and failure to completely eliminate migraine attacks have resulted in an estimated adherence to therapy of only 20%

after 1 year of treatment.¹⁹ It is estimated that episodic migraine may transition to chronic migraine (transformed migraine) at a rate of 2% in the US.²⁰ OnabotulinumtoxinA (Botox[®]) injection is indicated for prophylaxis of chronic migraine in adults.²¹

In 2018, the FDA approved the first calcitonin gene-related peptide (CGRP) inhibitors, erenumab-aooe (Aimovig), fremanezumab-vfrm (Ajovy), and galcanezumab-gnlm (Emgality), for preventative treatment of migraines in adults. The American Headache Society (AHS) released a position statement on integrating new migraine treatments into clinical practice.²² Unlike oral prophylaxis agents, the CGRP inhibitors do not require slow dose escalation, have a faster onset of therapeutic benefit, and have favorable tolerability profiles. The AHS recommends initiating CGRP inhibitors for migraine prophylaxis in patients ≥ 18 years of age with the following:

- Diagnosis of migraine (with or without aura) experiencing 4 to 7 monthly headache days with moderate disability and inability to tolerate or inadequate response to a 6-week trial of at least 2 oral prophylactic agents
- Diagnosis of migraine (with or without aura) experiencing 8 to 14 monthly headache days and inability to tolerate or inadequate response to a 6-week trial of at least 2 oral prophylactic agents
- Diagnosis of chronic migraine and either inability to tolerate or inadequate response to a 6-week trial of at least 2 oral prophylactic agents or at least 6 months of onabotulinumtoxinA treatment

According to the AHS response to CGRP inhibitor therapy should be assessed after 3 months (for monthly injections) or 6 months (for quarterly injections). Therapy should only be continued if clinically meaningful treatment benefit can be documented. The statement also addresses non-pharmacologic therapy, including neuromodulation and biobehavioral therapies.

Other therapeutic classes that are indicated for migraine prevention or with compelling data to support their use in this setting including, NSAIDs, anti-epileptic agents, beta adrenergic blockers, select triptans, and onabotulinumtoxinA (Botox), are not addressed in this therapeutic class review. This review will focus on CGRP inhibitors.

PHARMACOLOGY^{23,24,25}

Migraine onset is believed to involve stimulation of the trigeminovascular system leading to the release of inflammatory mediators during neurogenic inflammation and/or cortical spreading depression (CSD).²⁶ The neuropeptide, calcitonin gene-related peptide (CGRP) is expressed in the trigeminal ganglia and acts in both the periphery to enhance nociceptor sensitization and the central nervous system (CNS) to enhance sensory input, thereby intensifying pain perception. In the periphery, CGRP may cause endothelium- and nitric oxide-independent dilation of vascular beds, including intracranial arteries. Conflicting evidence suggests that elevated levels of CGRP may occur in external jugular blood flow during migraine attack. Moreover, administration of sumatriptan have been shown to normalize elevated CGRP levels in patients with migraine.

Erenumab-aooe (Aimovig), fremanezumab-vfrm (Ajovy), and galcanezumab-gnlm (Emgality) are humanized IgG4 monoclonal antibodies that inhibit the CGRP receptor. While, erenumab-aooe binds directly to the CGRP receptor and antagonizes its function, fremanezumab-vfrm and galcanezumab-gnlm bind to the CGRP ligand and blocks its binding to the CGRP receptor.

PHARMACOKINETICS^{27,28,29}

Drug	T _{max} (day)	Half-life (days)	Elimination
erenumab-aooe (Aimovig)	6	28	at low concentrations, predominantly through saturable binding to target (CGRP receptor); at higher concentrations, the through a proteolytic pathway
fremanezumab-vfrm (Ajovy)	5-7	31	enzymatic proteolysis into small peptides and amino acids
galcanezumab-gnlm (Emgality)	5	27	enzymatic proteolysis into small peptides and amino acids

T_{max} = time to maximum serum concentration; nr = not reported

CONTRAINDICATIONS/WARNINGS^{30,31,32}

All 3 products are contraindicated in patients with hypersensitivity to any component of the product. Hypersensitivity reactions including rash, pruritus, and urticaria have been reported; most events were mild to moderate in severity, but some led to therapy discontinuation or required corticosteroids therapy. Most occurred within hours of administration; however, some occurred days or weeks after administration.

DRUG INTERACTIONS^{33,34,35}

No drug-drug interactions are reported for any product in this class.

ADVERSE EFFECTS^{36,37,38}

Injection site reaction, including pain, erythema, and pruritus, have been reported with all 3 agents: erenumab-aooe (Aimovig) 5% to 6% (3% placebo); fremanezumab-vfrm (Ajovy) 43% to 45% (38% placebo); and galcanezumab-gnlm (Emgality) 18% (13% placebo). Muscle spasms/cramps and constipation were reported in ≤ 3% in patients treated with erenumab-aooe.

While anti-drug antibodies were detected for all 3 products, the available data were limited to determine their impact on safety and efficacy.

SPECIAL POPULATIONS^{39,40,41}

Pregnancy

There are no adequate data regarding developmental risks associated with the use of erenumab-aooe (Aimovig), fremanezumab-vfrm (Ajovy), or galcanezumab-gnlm (Emgality) in pregnant women.

Pediatrics

Safety and effectiveness of any CGRP inhibitor in pediatric patients have not been established.

Geriatrics

Clinical studies of any of the CGRP inhibitors did not include an adequate number of patients aged ≥ 65 years to determine whether elderly patients respond differently from younger patients.

Hepatic Impairment

Hepatic impairment is not expected to affect pharmacokinetics of CGRP inhibitors. No dedicated clinical studies to evaluate the impact of hepatic impairment have been conducted for erenumab-aooe, fremanezumab-vfrm, or galcanezumab-gnlm.

Renal Impairment

Renal impairment is not expected to affect pharmacokinetics of CGRP inhibitors. No formal clinical studies to evaluate the impact of renal impairment have been conducted for erenumab-aooe, fremanezumab-vfrm, or galcanezumab-gnlm.

DOSAGES^{42,43,44}

Drug	Dosage	Availability
erenumab-aooe (Aimovig)	70 mg SC once monthly; some patients may benefit 140 mg SC once monthly	70 mg/1 mL and 140 mg/1 mL single-dose prefilled SureClick® autoinjector (cartons contain one or two 70 mg/1 mL autoinjectors or one 140 mg/1 mL autoinjector)
fremanezumab-vfrm (Ajovy)	225 mg once SC monthly or 675 mg every 3 months (administer as 3 consecutive 225 mg injections) When switching dosage options, administer the first dose of the new regimen on the next scheduled date of administration	225 mg/1.5 mL single-dose prefilled syringe (carton contains 1 syringe)
galcanezumab-gnlm (Emgality)	240 mg SC (administered as 2 consecutive 120 mg injections) once as a loading dose, followed by 120 mg SC once monthly	120 mg/1 mL single-dose prefilled syringe and single-dose prefilled pen (carton contains 1 prefilled syringe or pen)

SC = subcutaneously

Erenumab-aooe, fremanezumab-vfrm, and galcanezumab-gnlm should be administered by SC injection only and may be self-administered with proper training. Inject in the abdomen, thigh, or upper arm. Do not inject into skin that is tender, bruised, red, or hard.

Erenumab-aooe, fremanezumab-vfrm, and galcanezumab-gnlm should be stored under refrigeration and placed at room temperature for at least 30 minutes prior to administration.

Erenumab-aooe (Aimovig) prefilled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions in latex-sensitive individuals.

CLINICAL TRIALS

Search Strategies

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all brand names in this class. Randomized, comparative, controlled trials performed in the US comparing agents within this class in an outpatient setting for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated,

predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Using these criteria, numerous studies were found. Data were further excluded based on the following characteristics: formulation or drug not available in US, single-blind or single-dose study. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

erenumab-aooe

In the double-blind STRIVE study, 955 patients ages 18 to 65 years with episodic migraine (defined as 4 to 14 migraine days per month), with or without aura, were randomized (1:1:1) to erenumab-aooe 70 mg, erenumab-aooe 140 mg, or placebo administered SC monthly for 6 months.⁴⁵ At baseline, mean migraine days per month (MDM) was 8.3 in the overall study population. By months 4 to 6, the mean MDM (primary endpoint) was reduced by 3.2 days in the 70 mg group (difference from placebo = -1.4; 95% confidence interval [CI]: -1.9, -0.9) and 3.7 days in the 140 mg group (difference from placebo = -1.9; 95% CI: -2.3, -1.4) compared to 1.8 days in the placebo group ($p < 0.001$ for each dose versus placebo). A reduction in mean MDM $\geq 50\%$ was achieved in 43.3% of patients in the 70 mg group (odds ratio [OR] = 2.13; 95% CI: 1.52, 2.98) and 50% of patients in the 140 mg group (OR = 2.81; 95% CI: 2.01, 3.94) versus 26.6% in the placebo group ($p < 0.001$ for each dose versus placebo). Serious adverse events were similar between all groups.

In the double-blind ARISE study, 577 patients with episodic migraine were randomized (1:1) to placebo or 70 mg erenumab-aooe administered SC monthly for 3 months, and 570 patients were included in the efficacy analysis.^{46,47,48} By 3 months, the mean MDM was reduced by 2.9 days in the treatment group compared to 1.8 days in the placebo group (treatment difference = -1; 95% CI: -1.6, -0.5; $p < 0.001$). A mean MDM $\geq 50\%$ reduction was achieved in 39.7% of patients in the treatment group versus 29.5% of patients in the placebo group (OR=1.59; 95% CI: 1.12, 2.27; $p = 0.01$). Safety and adverse events were similar between both groups.

The double-blind LIBERTY trial assessed erenumab-aooe in 246 adults with episodic migraine, with or without aura, who had failed 2 to 4 prophylactic migraine treatments in terms of efficacy and/or tolerability.^{49,50} Patients were randomized (2:1) to SC erenumab-aooe 140 mg (two 70 mg injections) or placebo every 4 weeks for 12 weeks. At week 12, 30% of patients in the erenumab-aooe group achieved mean MD $\geq 50\%$ reduction compared with 14% of patients in the placebo group (OR = 2.7; 95% CI, 1.4 to 5.2; $p = 0.002$). Safety and adverse events were similar between both groups.

A double-blind study (NCT02066415) was conducted in 667 adults with a history of chronic migraine (defined as ≥ 15 headache days per month with ≥ 8 migraine days per month), with or without aura. Patients were randomized (3:2:2) to placebo, erenumab-aooe 70 mg, or erenumab-aooe 140 mg given SC monthly for 3 months.⁵¹ At the end of the study, the mean MDM in both the 70 mg and 140 mg groups was reduced by 6.6 days compared to 4.2 days in the placebo group (treatment difference = -2.5; 95% CI: -3.5, -1.4; $p < 0.001$). A reduction in mean MDM $\geq 50\%$ was achieved in 39.9% of patients in the 70 mg group and 41.2% of patients in the 140 mg group versus 23.5% of patients in the placebo group ($p < 0.001$). Safety and adverse event profiles were similar between all groups.

fremanezumab-vfrm

The double-blind HALO EM study (NCT02629861) assessed the safety and efficacy of fremanezumab-vfrm in 1,875 patients with episodic migraine (defined as < 15 headache days per month).⁵² Patients were randomized (1:1:1) to fremanezumab-vfrm 225 mg monthly, fremanezumab-vfrm 675 mg every 3 months, or placebo monthly for 3 months. At baseline, mean MDM was 8.9, 9.3, and 9.1 in the fremanezumab-vfrm 225 mg and 675 mg groups and placebo group, respectively. By month 3, the mean MDM was reduced by 3.7 days in the 225 mg group and 3.4 days in the 675 mg group compared to 2.2 days in the placebo group ($p < 0.001$ for each dose versus placebo). A reduction in mean MDM $\geq 50\%$ was achieved in 47.7% of patients in the 225 mg group (difference from placebo = 19.8%) and 44.4% of patients in the 675 mg group (difference from placebo = 16.5%) versus 27.9% in the placebo group ($p < 0.001$ for each dose versus placebo). Serious adverse events were similar between all groups.

In the HALO CM study (NCT02621931), 1,130 adults with a history of chronic migraine (defined as ≥ 15 headache days per month) were randomized (1:1:1) to fremanezumab-vfrm 675 mg initially followed by 225 mg monthly, fremanezumab-vfrm 675 mg given every 3 months, or placebo once monthly for 3 months total.⁵³ The results showed that the mean number of MDM in the 225 mg group and the 675 mg group were reduced by 4.6 days and 4.3 days, respectively, compared to 2.5 days in the placebo group ($p < 0.001$ for both doses versus placebo). A reduction in mean MDM $\geq 50\%$ was achieved in 40.8% of patients in the 225 mg group and 37.6% of patients in the 675 mg group versus 18.1% of patients with placebo ($p < 0.001$ for both doses).

galcanezumab-gnlm

The 6-month, double-blind EVOLVE-1 (n=858) and EVOLVE-2 (n=915) studies evaluated efficacy and safety of galcanezumab-gnlm in adults with episodic migraine.^{54,55} Patients were randomized (2:1:1) to monthly SC placebo, galcanezumab-gnlm 120 mg, or galcanezumab-gnlm 240 mg. Patients in the 120 mg galcanezumab-gnlm arm received a 240 mg loading dose. The mean baseline migraine frequency in the studies was 9 MDM. In both trials, the primary endpoint of mean change from baseline in the number of MDM over 6 months was met for both galcanezumab-gnlm doses. In EVOLVE-1, treatment with galcanezumab-gnlm significantly reduced the mean MDM (both $p < 0.001$) by 4.7 days (120 mg dose) and 4.6 days (240 mg dose), compared with placebo (2.8 days); in EVOLVE-2, mean MDM were reduced by 4.3 days (120 mg) and 4.2 days (240 mg dose), and 2.3 days with placebo (both $p < 0.001$). Galcanezumab-gnlm was well tolerated.

The 3-month, double-blind REGAIN trial evaluated treatment with galcanezumab-gnlm in 1,113 adults with chronic migraine (defined as ≥ 15 headache days per month, of which ≥ 8 were migraines).⁵⁶ Patients were randomized (2:1:1) to monthly placebo, galcanezumab-gnlm 120 mg, or galcanezumab-gnlm 240 mg. All patients in the 120 mg galcanezumab-gnlm arm received a 240 mg loading dose. At baseline, mean number of monthly migraine headache days at baseline was 19.4. The primary endpoint of mean change from baseline in the number of monthly migraine headache days over 3 months was met for both galcanezumab-gnlm doses: reduction of 4.8 days (120 mg dose), 4.6 days (240 mg dose), compared to 2.7 days for placebo ($p < 0.001$ for both doses). Galcanezumab-gnlm was well tolerated.

SUMMARY

Migraine is a complex neurological condition that can involve debilitating headache and sensory changes. Migraine attacks are usually episodic (< 15 headache days per month), but some migraine sufferers experience chronic daily headaches at least 15 days per month, often with migrainous features.

Triptans have become the drugs of choice for treating acute migraine attacks with a response rate of about 60%. Studies suggest that 38% to 50% of migraineurs are candidates for preventive therapy. Indications for preventive therapy include ≥ 4 migraine attacks per month or ≥ 8 migraine days per month; acute medication overuse; and debilitating migraine. General first-line recommendations for either episodic or chronic migraine prophylaxis include oral medications such as select beta-blockers, anti-epileptics, and antidepressants; however, side effects and failure to completely eliminate headache pain result in low adherence to preventive therapy, estimated at 20% after 1 year of treatment. OnabotulinumtoxinA (Botox) injections are FDA-approved for chronic migraine prophylaxis only.

Calcitonin gene-related peptide (CGRP) may play a significant role in enhanced pain perception during a migraine attack. In 2018, the FDA approved the anti-CGRP monoclonal antibodies, erenumab-aooe (Aimovig), fremanezumab-vfrm (Ajovy), and galcanezumab-gnlm (Emgality). All agents in this new class of medications are shown to be effective and well tolerated for the treatment of episodic and chronic migraines. With proper training, each agent may be self-administered SC once monthly; galcanezumab-gnlm's dosing regimen includes an initial loading dose. Fremanezumab-vfrm may also be administered once every 3 months, which required 3 consecutive injections to deliver the entire dosage.

The American Headache Society (AHS) recommends incorporating CGRP inhibitors in preventive migraine therapy in patients experiencing episodic or chronic migraine who cannot tolerate or have had and inadequate response to a 6-week trial of at least 2 oral prophylactic agents; alternatively, intolerance or inadequate response to at least 6 months of onabotulinumtoxinA is appropriate in patients with chronic migraine.

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